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Efficacy and Cost of Atypical Antipsychotics in Treatment and Management of Dementia

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Introduction

The current population is living longer than ever before as a result of improved health care services; therefore, the size of the ageing population is increasing [1]. Dementia is emerging as one of the main conditions affecting the elderly population. According to the WHO report, in 2010, there were approximately 35.6 million people suffering from dementia worldwide. This figure continues to rise, doubling approximately every 20 years and it is estimated that this will soon rise to 65.7 million by 2030, and further to 115.4 million by 2050. Current incidence shows an individual is diagnosed with dementia every four seconds. This has substantial socioeconomic and financial implications on people globally and the societal costs associated with disease were estimated at US\$ 605 billion in 2010 [2].

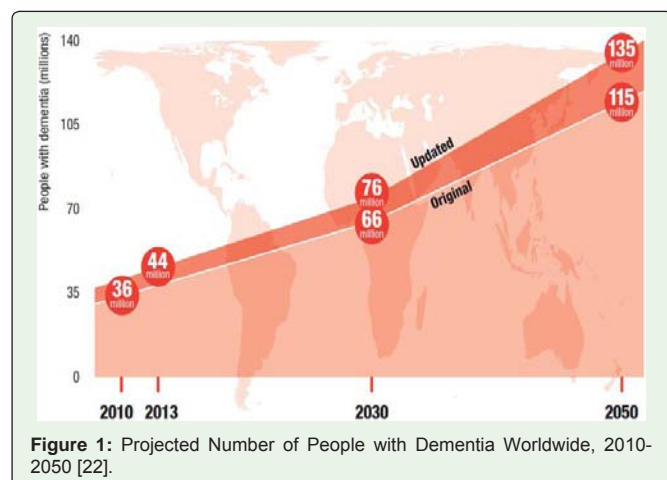
Alzheimer's Disease (AD) is the most common of dementia, closely followed by nonspecific degenerative dementia, whereas vascular dementia, dementia from Parkinson's disease and mixed dementia are observed less frequently [3]. Dementia has various impacts on the individual including a progressive loss of memory and deterioration in cognitive and behavioural functions [4]. Behavioural and psychological symptoms of dementia (BPSD) are commonly seen as the illness progresses. The disorder can be organized into four main groups: mood disorders, sleep disorders, psychotic symptoms and agitation [5]. Approximately 50-90% of people with dementia experience at least one symptom of behavioural disturbances at any one point [4,8-9]. Hence, this disorder has shown a significant impact on the quality of life of these individuals, their families and caregivers [10].

Both non-pharmacological and pharmacological interventions are used for the management of BPSD. In general, the non-pharmacological approach is recommended as the first-line intervention. The pharmacological approach should be initiated when the non-pharmacological approaches are unsuccessful; however, integrated interventions are advised for better management of dementia [11]. The management of patients with BPSD is quite complex and the most common pharmacological agents used include: antipsychotics, antidepressants, mood stabilizers, benzodiazepines and cognitive enhancers [1,11-12]. However, antipsychotic drugs are prescribed more frequently for BPSD as compared to other drug classes [1].

In 2005, U.S. Food and Drug Administration (US-FDA) launched an awareness campaign in regard to the adverse effects of Atypical Antipsychotics¹ (AAs) for the elderly BPSD population due to a 1.7% increase in the incidence of all-cause mortality risk [13]. Three years later, the FDA extended the warning to also include typical antipsychotics² [14]. Consequently, the trend of prescribing antipsychotics dropped from 2.3% in 2003 to 1.8% in 2011; however, the rate of prescribing AAs is reversing with an escalation from 0.37% to 0.64% [15]. Although there is controversial evidence in their effectiveness and safety, AAs are routinely prescribed for BPSD treatment [16].

Currently, there are no definitive treatments approved by the US-FDA for people with BPSD [5]. In addition, the treatment guidelines for BPSD remain controversial. Physicians have widely prescribed both typical and atypical antipsychotics drugs as the first-line interventions. Despite the high costs, AAs are more likely to be used for the treatment of BPSD, relative to typical drugs due to the increased efficacy and reduced side effect which includes preventing Extra Pyramidal Symptoms (EPS) in the geriatric population [1,4].

In clinical practice, the physicians have a variety of drug prescriptions and care plans in place for patients with BPSD. As a result, it is extremely important to determine the cost-effectiveness of AAs for use in BPSD as it not only affects the quality of life of patients and caregivers but also places additional burden on the health care system. Identifying which drug or combination of drugs is "most cost-effective" will indicate the most appropriate intervention and provide useful information on treatment plans for patients, caregivers, relatives and physicians. Also, the optimal treatment



pathway should prevent any severe impact on the quality of life of both patients and caregivers. The aim of this study is to explore and review the cost and effectiveness of using atypical antipsychotics in BPSD. Therefore it is pertinent that future research integrates pharmacological, epidemiological and health economic evaluation techniques in order to find most cost-effective treatment of BPSD for dementia patients.

Progression of Dementia

Dementia is a progressive brain disease associated with impairments in normal brain functioning. This includes cognitive, personality, and intellectual dysfunctions. It affects memory, thinking, language, learning ability, calculation, comprehension, judgment, and orientation. Thus, deterioration of the brain in this way can have a significant impact on people living with the condition, as well as on the society as a whole [2,17-19]. Alzheimer's Disease (AD) is the most common type of dementia, accounting for 50-70% of cases. Vascular Dementia (VaD), Dementia With Lewy Bodies (DLB), and Front Temporal Dementia (FTD) are also paramount categories of the disorder accounting for 20%, 10% and 2% of cases, respectively [9,17-18]. According to the World Health Organization, dementia can be classified into three stages: (i) the early stage (first or second year of the condition); (ii) the middle stage (second to fourth or fifth year with condition); and finally (iii) the late stage (fifth year and beyond) [2].

Behavioural and Psychological Symptoms of Dementia (BPSD)

Behavioural and psychological symptoms are commonly observed in the disease. These include neuropsychiatric and non-cognitive symptoms as well as behavioural disturbances [9,20]. Diagnosis of BPSD has no specific approach; therefore, clinical magnitude is more subjective than objective in patients with dementia. The clinical symptoms of BPSD present themselves as: agitation, apathy, anxiety, depression, delusion, hallucination, disinhibition, aberrant motor behavior, elation, irritability, and sleep and appetite changes [9,20-21]. BPSD tends to be more prevalent in the late stages of dementia. This results in distress among caregivers and patients, long term hospitalization, drug abuse, and other healthcare costs [21]. This alongside the decline in patients' and caregivers' quality of life makes BPSD a complex condition to manage.

Prevalence and Economic Impact of Dementia

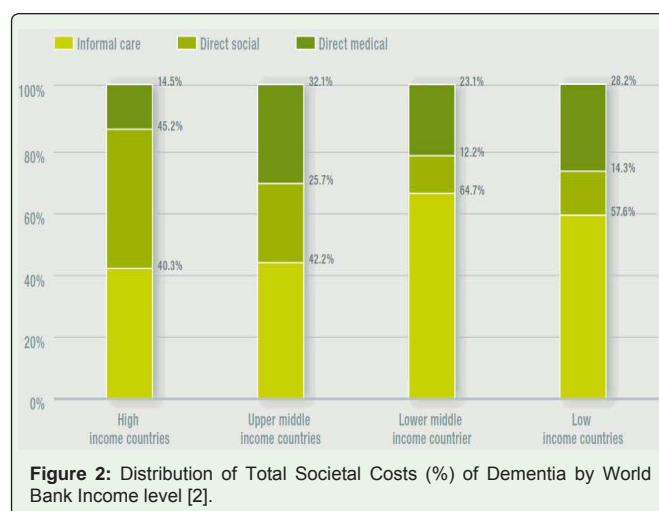
Dementia is a worldwide problem resulting from the rapid increase in size of the over 60 population which is estimated to reach 2 billion by 2050 [2]. It is predicted that nearly 7% (135 million) of this population will be diagnosed with dementia by 2050 (Figure 1) [22]. This will have significant social and economic impacts worldwide. There are three different types of costs associated with dementia care, namely informal care, direct social costs, and direct medical costs (Figure 2) and their proportion tends to vary according to the size and wealth of the country. In high income countries, the cost of informal care (provided by unpaid family members and friends) and direct social care both exceeded more than 40% of the total costs whereas, the direct medical cost was far less. Conversely, in lower-middle and low income countries there were significant greater costs related to informal care but not of direct social care. This shows that the burden of dementia management and care components impact on different socio-economic costs across the world including informal care wages and health and social care delivery costs.

Management of Behavioural and Psychological Symptoms of Dementia

People with dementia may experience BPSD at any point during its progression. This is associated with poorer health and quality of life outcomes for both patients and caregivers. As previously highlighted, the guidelines for the management of BPSD include both non-pharmacological and pharmacological approaches.

Non-Pharmacological Approach

The non-pharmacological approach is recommended as a first-line management for BPSD [9,11-12,23-25]. Treatment for behavioural disorders is administered after symptoms are reported. The most common approaches are environmental design, music therapy, light therapy, and educating caregivers on behavioural disturbances [9,23]. These also include the stimulation/activities and simple tasks for apathy [26-27]. Furthermore, Fujii et al. suggested that behavioural and psychological symptoms of caregivers (BPSC) which generally occurs as a result of BPSD in patients can impact on the relationship and emotions of the patient [28].



Pharmacological Approach

Implementation of pharmacological methods is necessary when non-pharmacological interventions are unsuccessful or when there is no response to the BPSD treatment [9,23]. There are several classes of drugs that have been utilized for the management of BPSD. The categories are listed below:

Anticonvulsants

There are studies associated with the use of Carbamazepine, sodium valproate, and gabapentin for the treatment of behavioural symptoms related to patients with dementia. However, evidence shows that treatment with valproate was ineffective in managing BPSD [23,29]. Carbamazepine revealed short-term effectiveness for agitated behaviour [23,30]. Although gabapentin alone and combined with psychotropic drugs showed efficacy for the BPSD treatment, however further research is required [23,31-32]. On the basis of current data, anticonvulsant drugs are not recommended for the treatment of BPSD associated with dementia [23,33].

Cholinesterase Inhibitors (ChEIs)

At present, there is evidence accounting for the benefits of ChEIs. Rodda et al. [34] showed that despite limitation of effectiveness data, ChEIs can be used for BPSD in Alzheimer's disease [35]. The US-FDA has approved donepezil, galantamine, and rivastigmine for treatment of symptoms of Alzheimer's disease; however, the recommendations of ChEIs are inconsistent in guidelines [11]. If behavioural symptoms still persist during ChEIs use, alternative drug classes may be considered as therapeutic options [24].

Antidepressants

Symptoms of depression are common in patients with dementia. Selective Serotonin Reuptake Inhibitors (SSRI) was observed for efficacy on depression [36]. Citalopram and sertraline had commensurate efficacy on agitated behaviour relative to risperidone or haloperidol. However, the guidelines around administration of antidepressants for behavioural disturbances are controversial, except when there is a co morbidity of depression [11,23,37].

Memantine or NMDA (N-Methyl-D-Aspartate)

The NMDA receptor antagonist (memantine) is currently the US-FDA approved drug for treatment of moderate to severe stages of Alzheimer's disease [37]. Nevertheless, the recommendation for BPSD is disputed in guidelines. The SIGN guideline highlighted that there is insufficient evidence for using memantine for the management of patients with BPSD [23]. In contrast, the NICE guidelines recommended memantine for non-cognitive symptoms in moderate and severe stages and discourage use of ChEIs and antipsychotics [35].

Antipsychotics

Antipsychotics are divided into two classes: typical and atypical. There are consistent guidelines for introducing antipsychotics for treatment of patients with BPSD, in particular for symptoms such as agitation, aggression, and psychosis [11,35]. Due to the adverse side effects, the NSW guidelines do not recommend conventional antipsychotics as a first-line drug [9]. Atypical antipsychotic drugs are

commonly prescribed for BPSD rather than typical antipsychotics. Drouillard, Mitanni and Chan noted that atypical antipsychotics were useful for managing BPSD related to agitation and aggression [38]. However, patients should be investigated prior to administration of these medications. Aripiprazole, olanzapine, and risperidone showed statistically significant effects for psychosis, agitation, and global behavioural symptoms in dementia [39]. And thus, Tampi et al. recommended that risperidone, aripiprazole and olanzapine should be considered as the first-line treatment [12].

The management of BPSD should integrate both non-pharmacological treatments and pharmacological treatments. Non-pharmacological approaches should be introduced as initial strategies. When non-pharmacological interventions show no effect, starting medication is considered appropriate. Atypical antipsychotics are considered to be beneficial as first-line drugs for the treatment of psychotic disorders in elderly people with dementia as they improve symptoms without causing adverse effects. However, the use of these drugs is controversial due to issues around drug safety and because the goal of pharmacological therapy is to reduce problematic disorders than merely eliminate symptoms. The concept of antipsychotic drugs is to "start slow, go slow". Thus, caregivers should be encouraged to take part in the decision-making process in patient care. Also, physicians should scrutinize the risks vs. benefits of pharmacological treatments to patients and their prescription should be considered on a case by case basis.

Efficacy and Cost-effectiveness of Atypical Antipsychotic Drugs for Dementia

The database search for the efficacy of atypical antipsychotic (risperidone, olanzapine, quetiapine and aripiprazole) drugs for dementia retrieved 2190 articles from MEDLINE, PsycINFO, and the Cochrane Library. Of these, 1075 articles were retrieved from MEDLINE, 754 articles retrieved from PsycINFO and 361 articles from the Cochrane Library. The titles were screened for inclusion and exclusion criteria. 2063 articles were excluded from the study due to their title. The remaining 127 articles were identified for further scrutiny. A further 81 articles were excluded after screening their abstracts. From the remaining 46 articles a further 26 were excluded due to duplication. 20 articles remained to undergo the next step (screening for full paper). Six articles were excluded due to not meeting the inclusion criteria. Another paper was excluded due to lack of access to the full-text.

Inclusion criteria were:

- 1) Participants: people with dementia, people with behavioural and psychological symptoms of dementia;
- 2) Interventions: atypical antipsychotic, risperidone, olanzapine, quetiapine and aripiprazole for treatment of dementia, Alzheimer's disease, behavioural and psychological symptoms of dementia and neuropsychiatric symptoms;
- 3) Study designs: randomized controlled trial, placebo controlled, double-blind, parallel-group trials comparing drugs with placebo; and
- 4) Outcomes: Behavioural Pathology in Alzheimer's disease Rating Scale (BEHAVE-AD), Clinical Global Impression

(CGI) scale, Neuropsychiatric Inventory (NPI), Cohen-Mansfield Agitation Inventory (CMAI), Brief Psychiatric Rating Scale (BPRS), Severe Impairment Battery (SIB), time for initial treatment to the discontinuation, and Mini-Mental State Examination (MMSE).

A further search for the cost-effectiveness of atypical antipsychotics from electronic databases was conducted in MEDLINE, the Centre for Reviews and Dissemination (CRD) (containing the National Health System Economic Database (NHS EED), the Database of Abstracts of Reviews of Effects (DARE), and Health Technology Assessment database) were searched. A total of 37 articles were retrieved. The titles were screened for inclusion and exclusion criteria. After screening the titles, 27 articles were excluded. A further seven articles were excluded after screening the abstracts, whilst another one was excluded as it was not in an English format which left two articles to be included in the study.

Inclusion criteria were:

- 1) Population: people with dementia, people with Alzheimer's disease;
- 2) Interventions: risperidone, risperdal, olanzapine, zyprexa, aripiprazole, abilify, quetiapine, and seroquel;
- 3) Study designs: comparison in terms of cost, and cost and health outcome, costs; and
- 4) Outcomes: QALYs, monetary costs, health benefits, health outcomes.

A systematic literature search identified only 13 clinical trial studies (with comparators) to demonstrate clinical effectiveness of atypical antipsychotics treatment of dementia with respect to risperidone, olanzapine, aripiprazole or quetiapine [40-52]. The results showed that the adverse events may offset efficacy associated with atypical antipsychotics for the treatment of BPSD. The serious side effects in senile dementia accounted for cerebrovascular events, extra pyramidal symptom, falls, somnolence, sedation, disinhibition, depression, incontinence, Parkinsonism, weight gain, orthostatic hypotension, dyskinesia and cognitive function impairment [46,53].

A cost-effectiveness of atypical antipsychotics retrieved only two quality studies [54-55]. Kirbach et al. focused on olanzapine for agitation and psychosis in Alzheimer's disease, based on the Markov state-transition model to estimate the cost-effective treatment. The results showed that olanzapine was cost-effective compared with an untreated group, for agitation and psychosis in AD in a community dwelling in the United States, using the US health system perspective [54]. However, the limitation of this study was that the cost variables entered into the model were derived from other studies and health utilities were deduced from schizophrenia studies. Rosenheck et al. used the cost-benefit analysis in a randomized controlled trial of second-generation antipsychotics and placebo for treating psychosis, agitation, or aggression in AD with a 9 months follow-up period. The findings demonstrated that risperidone, olanzapine and quetiapine showed no differences in effectiveness compared to the placebo, in a community dwelling in the United States [55].

Discussion

Despite the US-FDA warning in 2005 in relation to using

atypical antipsychotics for dementia due to increased incidence in cerebrovascular mortality of approximately 1.5 -1.7 times greater, the trend of prescribing atypical antipsychotic for patients with dementia has not receded. Atypical antipsychotics are significantly prescribed for the treatment of BPSD [56-57]. Recently, evidence showed that second-generation antipsychotic drugs had modest efficacy for the treatment of behavioural and psychological symptoms, namely agitation, aggression, psychosis, depression, anxiety. However, due to the limited and conflicting evidence for efficacy of atypical antipsychotic drugs their use for management of BPSD in patients with dementia is debatable.

Although atypical antipsychotics can be debated on the ground on effectiveness and adverse events, these drugs have been widely used for the treatment behavioural disturbance related to geriatric dementia [58]. This is because the severity of behavioural disturbance worsens as the disease progresses. This has potential impacts on morbidity, caregiver's general health, the burden of care, patients' and caregivers' distress, risk of harm to patients and caregivers, and costs of treatment. Consequently, it is important to weigh the risks and benefits when making judgments regarding the treatment and cost of behavioural problems in people with dementia. The pharmacological approaches are important and these are recommended when non-pharmacological methods fail. Despite the modest efficacy in the reduction of behavioural symptoms, the potential improvement of the condition has a considerable impact on the quality of life of patients and caregivers.

There is a significant lack of pharmacoeconomic research on using atypical antipsychotics for the treatment of dementia. Further comprehensive research should be carried out into this field. We have found a good number of studies exploring the effectiveness and cost-effectiveness of atypical antipsychotics for schizophrenia using a decision-analytical model. However, there were only a couple of studies which have focused on the use of AAs for dementia and that too with several limitations. Therefore, it is pertinent to undertake further systematic and comprehensive research on the safety and efficacy of atypical antipsychotics for the management of BPSD. This is essential in improving clinical practice and suggesting better pathways for dementia treatment as well as in mitigating the adverse impacts on the quality of life of patients and their caregivers.

¹Atypical antipsychotics are also called second-generation antipsychotics, or narcoleptic drugs such as clozapine, amisulpride, aripiprazole, asenapine, olanzapine, paliperidone, quetiapine, and risperidone.

²Typical antipsychotics are also known as conventional, classical or first-generation antipsychotics such as chlorpromazine, haloperidol, flupentixol, prochlorperazine, sulpiride and trifluoperazine.

(<https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency>)

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